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# Trends in gender difference in mortality after acute myocardial infarction<sup>☆</sup>

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## KEYWORDS

Myocardial infarction;  
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## Summary

**Background:** Progress in management of acute myocardial infarction (AMI) might have changed the effect of gender on mortality.

**Methods:** From May 1981 to November 2002, 1984 consecutive patients with AMI underwent emergency coronary angiography. They were divided into three groups in chronological order: group I (1981–1988,  $n = 564$ ); group II (1989–1995,  $n = 678$ ); and group III (1997–2002,  $n = 742$ ). Multi-variable analysis was performed using Cox's proportional hazard regression, adjusting baseline clinical and angiographical variables.

**Results:** There were 405 women (20%). Thrombolysis was most frequently performed in group I (50%), balloon angioplasty in group II (71%), and stent in group III (66%), with no difference in the allocation of reperfusion therapy between men and women. Three-year mortality was significantly higher in women than in men in group I (27% vs 18%,  $p = 0.03$ ) and group II (23% vs 15%,  $p = 0.048$ ). In group III, there was no significant difference in 3-year mortality (12% vs 10%,  $p = 0.66$ ) between women and men. Women were associated with higher age, more diabetes, more hypertension, fewer current smokers, and less previous infarction than men. Multi-variable analysis showed that sex was not an independent predictor of 3-year mortality in the three groups.

**Conclusions:** Women with AMI who were treated mostly with primary intervention using stent in the contemporary era had similar mortality to men.

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## Introduction

Acute myocardial infarction (AMI) is a leading cause of mortality in women as well as men in developed countries. Since the introduction of reperfusion therapy, several studies have demonstrated beneficial effects of thrombolysis [1]. Primary balloon angioplasty, as compared with thrombolysis, has been shown to decrease mortality after AMI [2]. Outcome after AMI has further improved with contemporary management, including stent implantation and ancillary medications [3]. During recent decades, many studies have reported that women have higher mortality after AMI than men [4–7]. Recently, some studies have reported that benefits from coronary intervention are larger in women than men, and that gender is not a predictor of mortality in patients undergoing primary coronary intervention [8,9]. However, no previous study compared gender difference in mortality after AMI between the thrombolysis era, the balloon angioplasty era, and the stent era. In this study, we investigated the temporal trends in mortality of women and men with AMI.

## Methods

From May 1981 to November 2002, 1984 patients with AMI who underwent coronary angiography within 24 h after the onset of symptoms at Hiroshima City Hospital, a tertiary referral institution, were prospectively registered. AMI was diagnosed by chest pain consistent with ongoing myocardial ischemia persisting longer than 30 min and concomitant electrocardiographic changes. Serum creatine kinase was measured every 3 h for at least 24 h, and peak creatine kinase value had to be more than twice the normal upper limit. They were divided into three groups in chronological order: group I (thrombolysis era: 1981–1988,  $n=564$ ); group II (balloon angioplasty era: 1989–1995,  $n=551$ ); and group III (stent era: 1997–2002,  $n=869$ ).

Emergency coronary angiography was performed in a manner as previously reported [10]. Selective coronary angiography was performed in multiple projections before the initiation of reperfusion therapy. Immediately after diagnostic angiography, reperfusion therapy was performed with coronary thrombolysis or coronary intervention, if appropriate. Not only primary coronary intervention, but also coronary intervention following thrombolytic therapy was categorized as coronary intervention. Coronary intervention was classified into con-

ventional balloon angioplasty and coronary stent implantation. The allocation of thrombolysis or coronary intervention was not randomized and was based on the physician's decision.

All coronary angiograms were reviewed by two angiographers without knowledge of the clinical variables. The perfusion status of the infarct related artery was determined in accordance with the thrombolysis in myocardial infarction (TIMI) study classification [11]. An initially occluded artery was defined as TIMI-0 or TIMI-1 flow before the initiation of reperfusion therapy. Successful reperfusion was defined as TIMI-3 flow on the final shot of the angiography. Multi-vessel coronary disease was defined as  $\geq 75\%$  stenosis in one or more vessels remote from the infarct artery. Collateral circulation was considered to be present if partial or complete filling of the infarct artery distal to the infarct lesion was present.

## Statistical analysis

Categorical data are reported as proportions and continuous data as mean values with standard deviations. Statistical analysis was performed with the chi-square test for categorical variables. The  $t$  test and ANOVA were used for continuous variables. Kaplan–Meier estimates were used to construct a long-term survival curve. Follow-up was achieved for up to 3 years by reviewing a clinical record or a form mailed to the patients or families, determining the vital status of the patients. Differences in 3-year mortality were assessed with the generalized Wilcoxon test. Cox proportional hazards regression was used to obtain odds ratio (OR) and 95% confidence interval (CI) for 3-year mortality. Multi-variable analysis was performed to obtain OR and 95% CI of women for 3-year mortality, adjusting age (model 1) or age, hypertension, diabetes mellitus, current smoking, Killip class, time to angiography, infarct location, initial occlusion of the infarct artery, collateral circulation, multi-vessel disease, and final reperfusion (model 2). We used the JMP statistical package (version 5.0.1 J). A significance level of 0.05 was used and two-tailed tests were applied.

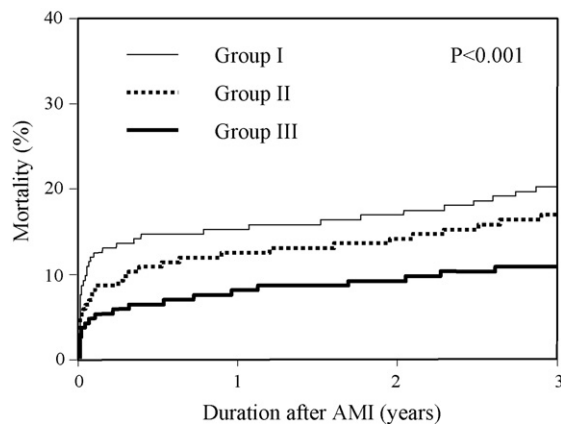
## Results

There were 405 women (20%) and 1579 men (80%). Baseline clinical and angiographic characteristics of women and men in group I, group II, and group III are shown in Table 1. Thrombolysis was most frequently performed in group I (50%), balloon angioplasty in group II (71%), and stent in group III (66%). On the

**Table 1** Baseline characteristics of the study patients

	Group I			Group II			Group III		
	Men	Women	<i>p</i> value	Men	Women	<i>p</i> value	Men	Women	<i>p</i> value
Number of patients (%)	446 (79)	118 (21)		448 (81)	103 (19)		685 (79)	184 (21)	
Age (years), mean (S.D.)	59 (11)	66 (9)	<0.001	61 (11)	67 (11)	<0.001	62 (11)	70 (9)	<0.001
Hypertension (%)	36	55	<0.001	33	50	0.003	38	54	<0.001
Diabetes mellitus (%)	19	25	0.17	21	30	0.04	26	33	0.04
Current Smoker (%)	67	30	<0.001	60	21	<0.001	58	23	<0.001
Previous infarction (%)	12	9	0.39	16	8	0.03	14	5	<0.001
Killip class 2–4 (%)	13	14	0.69	10	14	0.24	15	17	0.41
Time to angiography (h), mean (S.D.)	470 (4.7)	5.9 (4.7)	0.85	5.2 (4.7)	6.0 (5.7)	0.14	5.0 (5.2)	5.5 (5.2)	0.28
Anterior location (%)	56	50	0.24	50	50	0.93	49	49	0.89
Initial TIMI 0–1 (%)	76	78	0.69	79	76	0.41	76	72	0.28
Collateral circulation (%)	31	26	0.28	34	35	0.84	30	23	0.06
Multi-vessel disease (%)	33	44	0.02	38	38	0.92	41	39	0.57
Reperfusion therapy			0.39			0.09			0.04
Thrombolysis (%)	48	54		14	17		6	4	
Balloon angioplasty (%)	39	33		71	70		18	26	
Stent (%)	0	0		3	0		67	63	
Bypass surgery (%)	4	2		7	5		6	3	
Neither (%)	9	11		4	8		4	4	
Final TIMI 3* (n)	230/430	48/116	0.02	322/416	75/98	0.85	556/649	152/179	0.43
(%)	53	41		77	77		87	85	

\* Patients treated with bypass surgery (*n* = 101) were excluded.

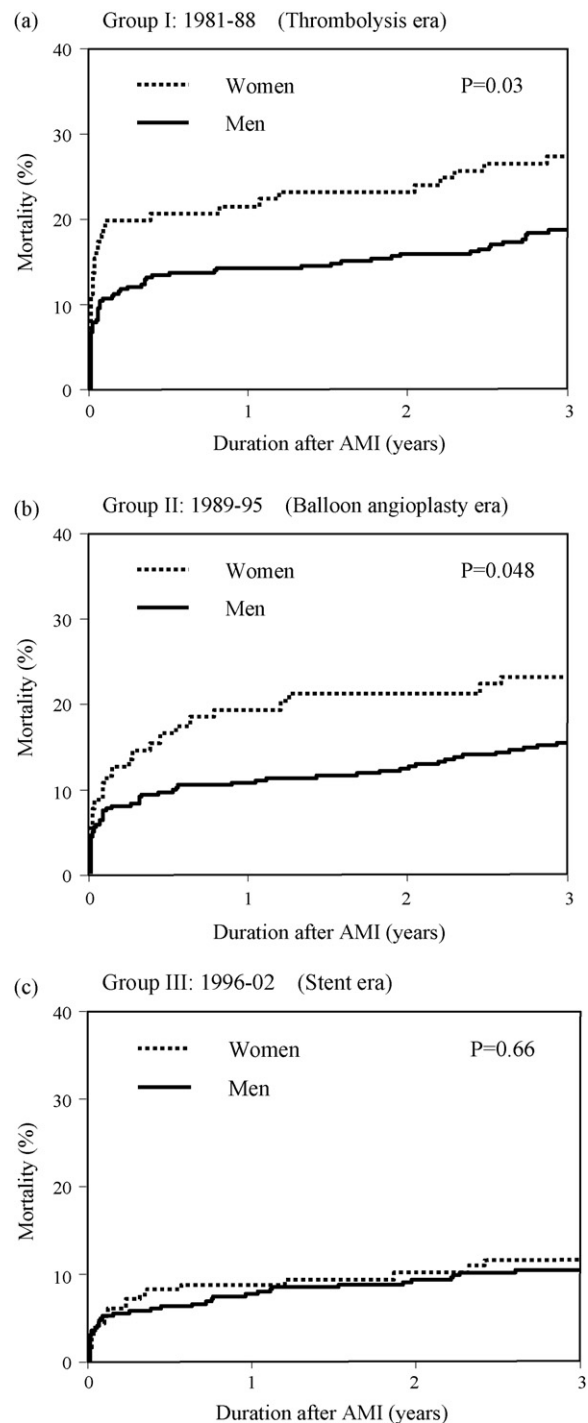


**Figure 1** Three-year mortality curves of group I, group II, and group III.

final angiography, the rate of achieving TIMI-3 flow improved in chronological order: 51% in group I, 77% in group II, and 87% in group III ( $p < 0.001$ ). The choice of reperfusion therapy was essentially similar between women and men. Women were associated with lower rate of achieving TIMI-3 flow in group I, but not in group II and group III.

When all patients were analyzed, women were associated with significantly higher 30-day mortality (10% vs 7%,  $p = 0.01$ ) and 3-year mortality (19% vs 14%,  $p = 0.009$ ). **Fig. 1** shows 3-year mortality curves of group I, group II, and group III. Mortality after AMI decreased significantly in chronological order; 30-day mortality was 12% in group I, 8% in group II, and 5% in group III ( $p < 0.001$ ). 3-year mortality was 20% in group I, 17% in group II, and 11% in group III ( $p < 0.001$ ). If gender difference in mortality was compared according to the reperfusion therapy used, women were associated with higher 3-year mortality after thrombolysis (25% vs 17%,  $p = 0.07$ ) and balloon angioplasty (21% vs 13%,  $p = 0.009$ ), but not after stent (10% vs 10%,  $p = 0.65$ ).

Three-year mortality curves of women and men in the three groups are shown in **Fig. 2**. In group I, 30-day mortality (19% vs 10%,  $p = 0.01$ ) and 3-year mortality (27% vs 18%,  $p = 0.03$ ) were significantly higher in women than in men. In group II, 30-day mortality was 11% in women and 7% in men ( $p = 0.20$ ). Three-year mortality was significantly higher in women than in men (23% vs 15%,  $p = 0.048$ ). In group III, there was no significant difference in 30-day mortality (4% vs 5%,  $p = 0.72$ ) and 3-year mortality (12% vs 10%,  $p = 0.66$ ) between women and men. Multi-variable analysis showed that sex was not an independent predictor of 3-year mortality in the three groups (**Table 2**).



**Figure 2** Three-year mortality curves of women (black bars) and men (white bars) in group I (a), in group II (b), and in group III (c).

## Discussion

This study showed that women with AMI had higher 3-year mortality than men in the thrombolysis era and the balloon angioplasty era. Women were associated with higher age and more co-morbid risk

**Table 2** Unadjusted and adjusted odds ratios for 3-year mortality

	Unadjusted odds ratio (95% CI)	Odds ratio adjusted for age (95% CI)	Odds ratio adjusted for age and other covariates (95% CI)
Group I	1.25 (1.01–1.53)	1.10 (0.88–1.34)	0.96 (0.72–1.22)
Group II	1.26 (0.99–1.58)	1.06 (0.83–1.34)	1.03 (0.78–1.34)
Group III	1.06 (0.81–1.35)	0.96 (0.73–1.23)	0.97 (0.71–1.29)

CI, confidence interval.

factors as compared with men. After adjustment for these variables, gender was not an independent predictor of 3-year mortality. This study also showed a progressive decrease in 3-year mortality, which was more obvious in women than in men. In the stent era, there was no significant difference in 3-year mortality between women and men with AMI.

Considerable numbers of studies have demonstrated that mortality after AMI was higher in women than in men. In the thrombolysis era, both 30-day and 3-year mortality were significantly higher in women than in men. The rate of achieving TIMI-3 flow was significantly lower in women than in men. Previous reports also have reported that women treated with thrombolytic therapy were at greater risk of complications and women with reinfarction following thrombolysis had more frequent early death than men [12,13]. Another possible explanation for the gender difference in mortality after AMI is difference in their risk profiles. Consistent with previous studies, women with AMI in our study constituted a high-risk population: women had higher age and more co-morbid risk factors. Most previous studies have reported that, after adjustment for age and co-morbid risk factors, gender was not an independent predictor of mortality after AMI. The third International Study of Infarct Survival (ISIS-3) reported that more than two thirds of the excess in mortality among women was eliminated by age adjustment and the remaining one third's excess by adjustment of other co-morbid risk factors [14]. This study also showed that unadjusted mortality after AMI was higher in women in the thrombolysis era, but there was no significant difference in mortality after adjusting for age and other risk factors.

In the early 1990s, several studies compared the usefulness of primary balloon angioplasty with thrombolysis and showed that primary balloon angioplasty increased the rate of successful reperfusion and decreased mortality over thrombolysis. In this study, the rate of achieving TIMI-3 in the balloon angioplasty era was 77% and there was no difference between women and men. There was still a tendency toward higher 30-day mor-

tality in women, but the difference was narrow and statistically non-significant. Although successful reperfusion was obtained in more than three quarters of the patients, the occurrence of early recurrent ischemia and reinfarction that abolish the beneficial effects of reperfusion therapy was considerably high. It has been reported that women suffer from such complications after plain balloon angioplasty more frequently than men [15]. Previous studies reported that mortality was higher in women undergoing primary balloon angioplasty for AMI than in men [16]. In this study, the difference in mortality gradually increased thereafter and 3-year mortality was significantly higher in women than in men.

Coronary stenting has the potential to overcome these limitations of balloon angioplasty. It has been reported that outcome after primary stent is favorable to primary balloon angioplasty, even if the angiographic findings are optimal or 'stent-like' after balloon angioplasty [17]. Such recent progress in reperfusion therapy along with progress in medical therapy has improved the outcome of patients with AMI in women as well as in men. There are conflicting data on the issue of higher mortality in women with AMI treated with primary stenting. The Controlled Abciximab and Devices Investigation to Lower Late Angioplasty Complications (CADILLAC) trial has reported higher mortality in women compared with men even after interventional treatment for AMI [18]. However, it was a randomized trial that consisted of selected patients. Mehilli et al. reviewed 1937 consecutive patients with AMI who were mostly treated with primary coronary intervention using stents [8]. Primary angioplasty was performed in 84.6% of women and 86.2% of men. Despite their more advanced age and greater prevalence of diabetes or hypertension, women had similar 1-year mortality to men. Similarly, in this study, primary coronary intervention was performed in 89% of women and 84% of men. Three-year mortality was not different between women and men in the stent era, despite higher age and more co-morbid risk factors in women than men. It has been reported that women were associated with higher incidence of dissection and vascular



entry site complications after percutaneous transluminal coronary angioplasty [15]. Use of stents dramatically reduced dissection after percutaneous coronary interventions and recent progress has permitted the use of smaller diameter catheters, which has reduced the incidence of vascular entry site complications.

Koek et al. have reported that gender difference in mortality after AMI became smaller among patients who underwent reperfusion therapy as compared to those without reperfusion therapy, but mortality was still higher even in women who underwent angioplasty/thrombolysis [19]. We also showed that women mostly treated with thrombolysis or balloon angioplasty had higher mortality than men. However, in the modern stent era, the improvement in outcome was more obvious in women than in men and there was no significant difference in 3-year mortality after AMI between women and men. Several studies have reported that evidence-based therapies, including primary coronary intervention, are underused in women with AMI [20,21]. It has been suggested that if women have access to the same quality treatment as men, their survival will be the same [22]. In the current study, all patients with AMI eligible for reperfusion therapy were encouraged to undergo coronary angiography. Since 1997 (group III), primary coronary intervention using stents was the preferred approach in both men and women, and mortality after AMI was no longer different between men and women. Aggressive management with primary angioplasty using stents for women may eliminate gender differences in mortality after AMI.

This is a retrospective study. However, all consecutive patients with AMI who underwent coronary angiography were prospectively included in a single-center registry. The allocation of reperfusion therapy was based on the physician's decision. But the choice of reperfusion therapy was essentially identical between women and men without sex-based difference in the use of primary coronary intervention. Recent progress in medical management along with reperfusion therapy, such as statins, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and beta-blockers, might have influenced the change in gender difference in mortality after AMI. However, our study did not include these data on ancillary medications. Prevalence of women was relatively smaller in this study (20%) as compared with previous studies from tertiary referral institutions (22–32%), suggesting selection bias of this study. Indeed, this study included only those patients who underwent coronary angiography within 24 h after the onset of AMI. However, it is still noteworthy that the

prevalence of women and the gender difference in age were consistent throughout the study period. Therefore, selection bias seemed not to be the reason why mortality of women after AMI in the stent era became as low as that of men. Small sample size is another limitation of this study. A large-scale nationwide registry should be warranted to assess gender difference in mortality after AMI in the contemporary stent era in Japan.

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